

Impact of Serum Adropin and Irisin in Iraqi patients with Congestive Heart Failure

MAHDE SALIH HAMAD¹, ENTEDHAR RIFAAT SARHAT^{1*}, THURAI RIFAAT SARHAT², KASIM SAKRAN ABASS³

¹Department of Basic Medical Science, Dentistry College, University of Tikrit, Tikrit, Iraq

²College of Education, University of Tikrit, Tikrit, Iraq

³Department of Pharmacology and Toxicology, College of Pharmacy, University of Kirkuk, Kirkuk, Iraq

Correspondence to Dr. Entedhar Rifaat Sarhat, Email: entedharr@tu.edu.iq

ABSTRACT

Background: The relations of adropin, and irisin concentrations to congestive heart failure (CHF) risk have not been comprehensively elucidated. We sought to study the markers of adropin, and irisin, both in control subjects and in CHF.

Methods: The study registered thirty four patients with CHF and thirty four healthy group. Fasting venous blood samples were collected from all cases. Serum adropin and irisin levels were analyzed using ELISA method. For all comparisons, statistical significance was defined by $p \leq .05$.

Results: Adropin, total cholesterol, and triglycerides parameters were found significantly high ($P < 0.001$) with the exception of irisin, and high-density lipoprotein- C which was significantly low ($P < 0.001$) in CHF patients.

Conclusion: The present work suggests a measurement of adropin and irisin level in serum samples is a potential marker for diagnosing of CHF.

Keywords: Adropin and irisin, congestive heart failure.

INTRODUCTION

Congestive heart failure (CHF) is a leading cause of cardiac morbidity and mortality. It is characterized by dyspnea, fatigue, and signs of volume overload, which may include peripheral edema and pulmonary rales. Data from the National Health and Nutrition Examination Survey III (NHANES III) estimate that 4.7 million people in the United States are treated for CHF each year. CHF has a poor prognosis despite new improvements in its management. Activation of the sympathetic nervous system is one of the major pathophysiological abnormalities in HF patients. Myocardial ischemia may occur either from increased demand of oxygen by the myocardium, or decreased oxygen supply to the myocardium, or both¹⁻³.

The adipose tissue is a complex, essential, and highly active metabolic and endocrine organ⁽⁴⁾, that releases many metabolically active peptide hormones, bioactive cytokines, chemokines and adipokines, including leptin, visfatin, resistin, apelin, omentin, sex steroids, and various growth factors are cell signaling proteins^{5,6}.

Apelin is a novel adipocytokine produced by white adipose tissue, that is synthesized by endothelial cells and exerts its functions through autocrine and paracrine pathways by binding to endogenous ligand of the G-protein coupled receptor expressed absolute presence in most types of cells in the heart, including myocytes, smooth muscle cells and fibroblasts^(5,7). The apelin and its receptor (APJ receptor) is one of the molecular systems which counteracts the negative effects of aldosterone on the myocardial cells and limits the inflammatory reactions and the oxidative⁸.

Adropin is a new peptide hormone, its expression in a human liver cell line (HepG2) is suppressed following the activation of liver receptor (LXRα), suggesting sensitivity to carbohydrate and lipid metabolism⁽⁹⁾, regulation of energy metabolism, insulin resistance, and endothelial functions, regulating angiogenesis and increasing blood flow and capillary density in a model of hind limb ischemia¹⁰.

Energy metabolism and insulin resistance-related proteins, such as leptin, adiponectin, ghrelin and tumor necrosis alpha, have been well-studied, and recently an additional exercise-induced peptide known as irisin has been identified^{11,12}. Irisin, with 112 amino acids (12587 Da), is a cleaved and secreted fragment of fibronectin type III domain containing 5 (FNDC5)¹³, an adipokine and myokine, and exhibits autocrine and paracrine effects that is released from the liver, testis, spleen, gut, kidney, heart, nerves, skeletal muscles and skin. that plays a pivotal role in mitochondrial function, metabolic and energy expenditure regulation¹⁴.

METHODS

Subject: One hundred fifty individuals with age ranged between (20-45) year were enrolled in this study. They were divided into two groups: group one (G1) consisted of 30 patients with CHF. group (G2) consisted of 30 healthy group. The patients attended the Tikrit Teaching Hospital / Tikrit / Iraq during June 2018 to August 2019. Echocardiographic measurements were performed according to guidelines and recommendations by the European Association of Echocardiography¹⁵.

Blood Sample Collection

Five milliliters of blood samples were drawn from an antecubital vein by careful venipuncture using a 21-gauge needle without stasis between 08.00 and 10.00 a.m. after a resting time of 30 min and a fasting period of 12 h. Routine biochemical parameters were determined by standard methods.

Biochemical analyses: Adropin and irisin levels were analyzed using enzyme linked-immunosorbent assay (Catalog No. CK-E90905, Hangzhou East biopharm Co. Ltd.) was used to determine Irisin levels, following the manufacturer's instructions. we also measured glucose, triglyceride, cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein levels in both patient and control groups.

The results are expressed as mean \pm S.D. and all statistical calculations were made by applying paired Student's t-test with the significance level at $P < 0.05$.

RESULTS

Adropin, Irisin, and lipid profile of patients in CHD was significantly different from that of the controls; though within the desirable levels (Table 1).

The Apelin level in serum was substantially decreased in the CHF group as compared with the control group (1.2 ± 0.73 vs 2.7 ± 0.79 ng/ml: $p < 0.001$).

Serum adropin and **irisin**, levels were significantly elevated in CHF patients as compared to healthy controls (11.56 ± 1.09 vs 5.75 ± 1.27 ng/mL: $p < 0.05$), and (0.497 ± 0.145 vs 0.288 ± 0.138 μ g/mL:) respectively.

Table 1: Mean \pm S.D. Adropin, Irisin, and lipid profile of patients in CHD

Parameter	Control	CHF	P value
Apelin (ng/ml)	2.7 ± 0.79	1.2 ± 0.73	< 0.001
Adropin (ng/mL)	5.75 ± 1.27	11.56 ± 1.09	< 0.05
Irisin (μ g/mL)	0.288 ± 0.138	0.497 ± 0.145	< 0.05
Total cholesterol (mmol/l)	4.35 ± 0.120	7.16 ± 0.147	< 0.0001
TG (mmol/l)	1.15 ± 0.071	3.41 ± 0.11	< 0.0001
HDL-C (mmol/l)	1.09 ± 0.035	0.62 ± 0.022	< 0.0001

TC and TG levels showed a significant increase while HDL-C was significantly decreased among the cases. Mean and standard deviation values of TC in the cases was 7.16 ± 0.147 mmol/l vs. 4.35 ± 0.120 mmol/l in the controls ($p < 0.0001$). TG level in the cases was 3.41 ± 0.11 mmol/l vs. 1.15 ± 0.071 mmol/l in the controls ($p < 0.0001$). HDL-C level in the cases was 0.62 ± 0.022 mmol/l compared to 1.09 ± 0.035 mmol/l in the controls ($p < 0.0001$).

DISCUSSION

Biochemical changes in cardiac myocytes, interstitium, or both, associated with release of various biochemical markers like cytokines, neurohormones (renin-angiotensin-aldosterone and adrenergic nervous systems), enzymes, etc., which can be estimated in blood¹⁶.

Under normal conditions apelin and APJ are expressed in cardiac myocytes. It have many actions ranging from inotropy to vasodilatory properties, both directly in a nitric oxide- and endothelium-dependent manner and indirectly through control of vasopressin release in the central nervous system^{17,18}.

Serum level of Apelin was found to be significantly reduced in patients with CHF compared to control group due to failing cardiac muscle could increase production of this powerful inotropic peptide as a compensatory mechanism to augment inotropic capacity and maintain cardiac output¹⁹.

Adropin may be a novel and effective serum marker for the evaluation of endothelial function²⁰. It increases nitric oxide release and activates eNOS, so it directly affects the endothelium and has a protective role for endothelium via up regulating eNOS²¹.

Our study found a decrease in the activity of adropin could be due to endothelial dysfunction plays a crucial role in the maintenance of vascular homeostasis, and endothelial dysfunction contributes to the development and progression of cardiovascular diseases²². Yu *et al*²³ have reported reduced adropin levels in cases of acute myocardial infarction and examined the role of adropin in MI.

Cardiac muscle produces more irisin than skeletal muscle. Irisin is mainly produced within heart and skeletal muscle⁽²⁴⁾, it is facilitate the conversion of brown adipose tissue that dissipates energy in the form of heat into white adipose tissue that serves as an energy depot²⁵.

In our study, however, we found statistically significant difference in irisin levels in the CHF patients and the control group (< 0.05). The exact mechanism by which irisin is involved in CHF is unclear. The elevated circulating irisin levels in patients with risk for cardiovascular diseases or MACE have been considered as a state of irisin-resistance. In addition, as heart might be a major producer of irisin, the uncoupling properties of irisin may result in more ATP loss and lead to poor prognosis of cardiovascular diseases²⁶. Aronis *et al*²⁷ reported that increased irisin levels predict the development of major cardiovascular events, especially unstable angina, in patients with CAD after percutaneous intervention (PCI). Hanatani *et al*²⁸ also reported that irisin is a novel biomarker providing prognostic information in patients with heart failure with reduced ejection fraction.

Both basic science and clinical studies support the inverse relationship between HDL-C levels and atherosclerosis. HDL enhances the reverse cholesterol transport and has anti-oxidative, anti-inflammatory, antithrombotic, and vasoprotective effects²⁹.

This study demonstrated a significant increase in cholesterol, TG, LDL-C, with the exception of significant decrease in the HDL in CHD group. Elevated total cholesterol is related to increased blood pressure, increased arterial stiffness and decreased vascular compliance, and an increased left ventricular mass and wall thickness. Decreased HDL-C concentrations are associated with increased left ventricular mass, decreased diastolic function and a lower ejection fraction in people with both normal and stenosed coronary arteries^(30,31).

CONCLUSION

These results revealed that adropin might represent as a potential biomarker for diagnosis of and severity CHF.

Conflict of Interests: The authors of this paper declare that he has no financial or personal relationships with individuals or organizations that would unacceptably bias the content of this paper and therefore declare that there is no conflict of interests.

Source of Funding: The authors have no sources of funding, so it is self-funding research.

Ethical Approve: We declare that the study does not need ethical approval.

REFERENCES

- Karabacak M., Dogan A., Tayyar S.c. Bas H.A. Oxidative Stress Status Increase in Patients with Nonischemic Heart Failure. *Med Princ Pract* 2014;23:532-537.
- Entedhar R. Sarhat, Moayad MY Al-Anzy, Mutaz S. Ahmeid, Thuraia R. Sarhat. Characteristic Abnormalities in Serum Biochemistry during Congestive heart failure. *Tikrit Medical Journal – June-2018;Vol(24) No(1):69 – 77.*
- Entedhar R. Sarhat, Siham .A. Wadi,Ayhan R. Mahmood. Measurement of the Levels of Salivary Lipocalin-2 and C - reactive protein in Women with Polycystic Ovarian Syndrome .*Tikrit Journal for Dental Sciences* 7(1) (2019)31-35
- Anas Qahtan Hamdi, Entedhar R. Sarhat, Nagham Hasan Ali. Evaluation of Lipocalin-2 and Visfatin, and Vitamin (D,C, and E) in Serum of Diabetic Patients with Chronic Periodontitis . *Indian Journal of Forensic Medicine & Toxicology*.2021.
- Entedhar Rifaat Sarhat. Acute Myocardial Infarction: Melatonin, Apelin, and Visfatin as Predictors of Disease .*Diyala Journal of Medicine*.2017; 11(13):11-17.
- Entedhar R. Sarhat, Mahde S. Hamad, Salim J.Khalaf. Leptin , Adiponectin ,and Interleukin-6 Levels Among Beta Thalassaemia Patients. *Science advance* . 2020;14(127): 99-105.
- Sarhat ER, Rmaid ZJ, Jabir TH (2020) Changes of salivary interleukine17, Apelin, Omentin and Vaspn levels in normal subjects and diabetic patients with chronic periodontitis, *Ann Trop Med & Pub Health*; 23:S404. DOI: <http://doi.org/10.36295/ASRO.2020.23118>.
- Cerasela Mihaela Goidescu, Florin Petru Anton, Daniel Corneliu Leucuța , Petru Adrian Mircea , Luminița Animate Vida-Simiti. Serum level of apelin-13 negatively correlated with NT-proBNP in heart failure patients. *Revista Română de Medicină de Laborator*.2016; 24(4):300-412.
- Joseph R. Stevens , Monica L. Kearney , Marie-Pierre St-Onge, Kimber L. Stanhope, Peter J. Havel,Jill A. Kanaley , John P. Thyfault7 , Edward P. Weiss8 , and Andrew A. Butler. Inverse Association Between Carbohydrate Consumption and Plasma Adropin Concentrations in Humans. *Obesity* .24(8); 2016: 1731- 1740.
- Akcilar R, Emel Koçak F, Şimşek H, et al. The effect of adropin on lipid and glucose metabolism in rats with hyperlipidemia. *Iran J Basic Med Sci*. 2016;19(3):245-51.
- Entedhar R. (2015).Study the levels of Leptin, and Adiponectin with Paraoxonase in Obese Individuals (male & female).*Tikrit J.of Pure Science*.20 (2):16717.
- Shatha H Ali, Ali MA AL-Nuaimi, Bushra J AL-Musawi. Serum irisin and leptin levels in obese and non-obese women with polycystic ovary syndrome with reference to glucose homeostasis. *Int J Pharm Pharm Sci* 2016;8(10):276-283.
- Wen Deng. Association of Serum Irisin Concentrations with Presence and Severity of Coronary Artery Disease. *Med Sci Monit*, 2016; 22: 4193-4197
- Suleyman Aydin. Three new players in energy regulation: Preptin, adropin and irisin. 56(1), 2014, 94-110.
- Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *J Am Soc Echocardiogr* . 2005; 18: 1440–1463.
- Sarhat Entedhar Rifaat, Khalaf Salim Jasim, Hamad Mahde Salih. A Study of Some biochemical Parameters in blood Serum of Patients with congestive Heart Failure. *Indian Journal of Public Health Research & Development*.2019: 10(5); 413- 418.
- Wysocka MB, Pietraszek-Gremplewicz K and Nowak D (2018) The Role of Apelin in Cardiovascular Diseases, Obesity and Cancer. *Front. Physiol.* 9:557. doi: 10.3389/fphys.2018.00557.
- Parikh VN, Liu J, Shang C, Woods C, Chang AC, Zhao M, Charo DN, Grunwald Z, Huang Y, Seo K, Tsao PS, Bernstein D, Ruiz-Lozano P, Quertermous T, Ashley EA. Apelin and APJ orchestrate complex tissue-specific control of cardiomyocyte hyper- trophy and contractility in the hypertrophy-heart failure transition. *Am J Physiol Heart Circ Physiol* 315: H348 –H356, 2018.
- Duman, Hakan et al. "The Relationship between Serum Apelin Levels and the Severity of Calcific Aortic Stenosis." *Acta Cardiologica Sinica* vol. 34,3 (2018): 259-266.
- Gozal, D. et al. Circulating adropin concentrations in pediatric obstructive sleep apnea: potential relevance to endothelial function. *J Pediatr*.2013. 163, 1122–1126.
- Lovren F, Pan Y, Quan A, et al. Adropin is a novel regulator of endothelial function. *Circulation*2010;122(11 Suppl):S185–S192.
- Celik A, Balin M, Kobat MA, Erdem K, Baydas A, Bulut M, et al. (2013). Deficiency of a new protein associated with cardiac syndrome X; called adropin. *Cardiovasc Ther*, 31(3): 174–8.
- Yu HY, Zhao P, Wu MC, Liu J, Yin W. Serum adropin levels are decreased in patients with acute myocardial infarction. *Regul Pept*. 2014;190-191:46-9.
- Adela, Ramu & Banerjee, Sanjay. Novel Biomarkers to Understand Cardiovascular Complications in Diabetes.2016; 93-117. 10.5772/62595.
- Sahin K, Yeniocak S, Sarac F, Ayta S, Elevli M, et al. An Investigation of Serum Irisin Levels in Children Experiencing Convulsive Seizures, *Iran J Pediatr*. 2018 ; 28(5):e63642.
- Aydin S, Kuloglu T, Aydin S, Eren MN, Celik A, Yilmaz M, Kalayci M, Sahin İ, Gungor O, Gurel A, Ogeturk M, Dabak O: Cardiac, skeletal muscle and serum irisin responses to with or without water exercise in young and old male rats: cardiac muscle produces more irisin than skeletal muscle. *Peptides* 2014; 52: 68-73.
- Aronis KN, Moreno M, Polyzos SA, Moreno-Navarrete JM, Ricart W, Delgado E, de la Hera J, Sahin-Efe A, Chamberland JP, Berman R, Spiro A 3rd, Vokonas P, FernándezReal JM, Mantzoros CS. Circulating irisin levels and coronary heart disease: association with future acute coronary syndrome and major adverse cardiovascular events. *Int J Obes (Lond)*. 2015; 39(1):156–61.
- Shinsuke Hanatani , Yasuhiro Izumiya , Yuichi Kimura , Yoshiro Onoue , Satoshi Araki , and Hisao Ogawa.Circulating Irisin is a Novel Biomarker Providing Prognostic Information in Patients With Heart Failure With Reduced Ejection Fraction.*Circulation*. 2018;130(2):A12549.
- Rambabu Kondreddy, Ali Chenak,Uma Shankar Akula, Addison garabet, Shakila Sri Kumar, Abdalla M Jarari, Jagannadha Rao Peela. (2012). Study of Lipid Profile in Coronary Heart Disease patients in Libya. *JOURNAL OF BIOMEDICAL SCIENCES*. 1 (4:3);1-9.
- Chen Y, He XM, Meng H, et al. Relationship between lipids levels and right ventricular volume overload in congestive heart failure. *J Geriatr Cardiol*. 2014;11(3):192-9.
- Entedhar Rifaat Sarhat, Thuraia R. Sarhat, Dina N. Tawfeeq. (2016). Study of serum levels of Melatonin, Paraoxonase, Oxidative stress in Iraqi patients with Acute Myocardial Infarction. *EUROPEAN ACADEMIC RESEARCH – IV(1)*.112-131.